

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/12	A1	(11) International Publication Number: WO 98/05302 (43) International Publication Date: 12 February 1998 (12.02.98)
(21) International Application Number: PCT/GB97/01502 (22) International Filing Date: 3 June 1997 (03.06.97) (30) Priority Data: 9616237.5 1 August 1996 (01.08.96) GB (71) Applicant (for all designated States except US): NORTON HEALTHCARE LIMITED [GB/GB]; Gemini House, Flex Meadow, Harlow, Essex CM29 5TJ (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): MILLER, Fiona [GB/GB]; Norton Healthcare Limited, Gemini House, Flex Meadow, Harlow, Essex CM29 5TJ (GB). (74) Agent: PAWLYN, Anthony, Neil; Urquhart-Dykes & Lord, Tower House, Merrion Way, Leeds LS2 8PA (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: AEROSOL FORMULATIONS (57) Abstract The replacement of chlorofluorohydrocarbon propellants in medical aerosols is of the utmost importance to the pharmaceutical industry. A number of formulations have been investigated. The present invention provides a medical aerosol formulation comprising a particular medicament, a fluorocarbon propellant and 6 to 25 % w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant. Cannisters suitable for delivering such a pharmaceutical formulation are also provided.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

-1-

AEROSOL FORMULATIONS

This invention relates to pharmaceutical formulations for inhalation aerosols. The Montreal Protocol on ozone depleting gases has made the reformulation of existing pharmaceutical aerosols for inhalation treatment containing chlorofluorohydrocarbon propellants, a matter of urgency for the pharmaceutical industry.

A number of hydrofluorocarbons (HFCs) have been the subject to toxicological testing and two in particular P134a (1,1,1,2-tetrafluoroethane) and P227 (1,1,1,2,3,3,3-heptafluoropropane) have been identified as safe for use in pharmaceutical aerosols.

A number of patent applications have been submitted in this field, the first being EP 372777, which discloses the use of four component mixtures, comprising a medicament, a surfactant, P134a and a co-solvent of higher polarity than the P134a, in the form of a solution or a suspension.

As inhalation aerosols are meant for administration to the lung, it has long been accepted that such formulations should contain as few ingredients as possible, to avoid putting unnecessary materials into the lung.

Historically, despite EP 372777, solution aerosols contained only medicament, propellant or propellant mixtures and, if necessary, co-solvent, usually ethanol, eg US 2868691. The use of a surfactant was normally unnecessary for solution aerosols. However, historically medicinal suspension aerosols have contained a surfactant eg US 3014844, as it was considered that the use of a surfactant was necessary to prevent agglomeration of particles, to prevent adhesion to the sides of the canister, and to aid valve lubrication and prevent valve sticking.

However it was disclosed in EP 616525 that it is possible to prepare medicament suspensions in a hydrofluorocarbon without the need for a surfactant, if a polar co-solvent was added. The normal co-solvent ethanol, has well established

-2-

physiological actions and being a pure absorbable liquid eliminates any possibility of residues remaining in the lung. Irritation or possible toxicity from the surfactant, many of which are mixtures of similar compounds, are avoided.

EP 616525 specifically limits the polar co-solvent level to 0.01 to 5% w/w and in particular states (page 3, line 55) that the preferred level is about 0.1% w/w.

According to a first aspect of the present invention there is provided a medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

According to a second aspect of the present invention there is provided a medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

According to a third aspect of the present invention there is provided a canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

It has now been surprisingly found that higher levels of alcohol have beneficial results. Levels of 6% or more of ethanol produce satisfactory suspensions, which do not agglomerate on standing, and on reshaking produce finely dispersed medicament. It is believed that the higher levels of alcohol reduce the degree of deposition on the inside of the can. This is a very desirable feature. In addition, the use of these larger percentages of ethanol enables a much cheaper production process.

Medicinal aerosols can be filled either with one dose of liquid containing all of the ingredients mixed together or by

-3-

a two dose process where the first dose contains the medicament and all other ingredients, including co-solvents, surfactants, if any, ancillary compounds eg flavours, if any, and some times some of the propellant followed by a second dose of pure propellant. This two dose fill has major cost advantages in that the volume of mix for a fixed number of cans is significantly smaller enabling the use of smaller mixing vessels. In particular, with the use of the new HFC propellants, which have lower boiling points than the old CFC propellants, the use of a one dose fill may involve the use of cooled pressurised vessels to prevent evaporation of the propellant gas during mixing and filling. With the new formulations with added extra co-solvent a first mix of just medicament suspended in the co-solvent can be used, followed by a second dose of pure propellant. This means that the propellant can be dosed directly from a holding tank into the can without any need to mix and store with the other ingredients. For example a mix weight of 1g of medicament and co-solvent can be followed by 7.5g of propellant. In this way the volume to be mixed is reduced from 8.5g to 1g. All the examples in EP 616525 are of laboratory scale, where the handling problems are much easier, but all the formulations described are such that it would not be practicable to fill in two doses without mixing the propellant, as is the case with the present disclosure.

The description of the filling method given on page 5 lines 2-13 indicates that only a one dose filling method is envisaged.

In all cases of the present invention the medicament consists of a particle size suitable for inhalation into the lung and will thus be less than 100 microns, desirably less than 20 microns and preferably in the range of 1-10 microns, normally with a mean particle size 1-5 microns.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant.

-4-

Appropriate medicaments may thus be selected from, for example, analgesics, eg codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, eg diltiazem; antiallergics, eg cromoglycate, ketotifen or nedocromil; anti-infectives, eg cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, eg methapyrilene; anti-inflammatories, eg beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, eg noscapine; bronchodilators, eg ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tolubuterol, orciprenaline; diuretics, eg amiloride; anticholinergics, eg ipratropium, atropine or oxitropium; hormones, eg cortisone, hydrocortisone or prednisolone; xanthines, eg aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, eg insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (eg as alkali metal or amine salts or as acid addition salts) or as esters (eg lower alkyl esters) or as solvates (eg hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Preferred are those compounds which are also substantially insoluble in the co-solvent. Particularly preferred as medicament is salbutamol either as base or as a salt and especially salbutamol sulphate.

Co-solvents may be selected from polar alcohols and polyols, particularly C₂-C₆ aliphatic alcohols and polyols, such as propylene glycol, and preferably ethanol. Levels of co-solvent will be between 6% and 25% w/w of the total canister content, preferably between 10-15% w/w of canister content.

The propellant may be a hydrofluorocarbon, particularly P134a or P227. Other hydrofluorocarbons or hydrocarbons or aliphatic gases (eg Dimethylether) may be added to modify the

-5-

propellant characteristics as required.

The product is preferentially produced by weighing the active medicament and suspending it in the co-solvent. The appropriate amount of suspension is then dosed into the can, followed by a second dose of propellant or propellant mix. However, a one shot fill or any other equivalent method may be employed.

The normal medicinal product on the market has an actuator with spray orifice diameter of about 480 microns. However, with the larger percentages of ethanol envisaged in this invention, it is desirable that the co-solvent evaporates from the particles as rapidly as possible.

This is achieved by reducing the aperture to between 100-300 microns, which for the same dosage or drug, gives more rapid evaporation of the co-solvent. A particularly preferred embodiment of the invention is a combination of a level 10-15% co-solvent (normally ethanol) with a stem aperture of 150-250 microns.

The invention is further described by means of example but not in any limitative sense.

Example

Salbutamol Sulphate	0.03g
Ethanol	0.97g
Tetrafluoroethane (P134a)	7.5g

The salbutamol sulphate previously micronised to give over 90% of particles below 10 microns was weighed out and added to the ethanol. The suspension was mixed until it was smooth and uniform and then filled into the aerosol canister. The metering valve assembly was crimped (preferably vacuum crimped) on the canister and then the P134a was filled through the valve. The valve capacity is such as to deliver 100 micrograms of salbutamol, as salbutamol sulphate per actuation.

A particularly preferred use of such a canister is in a patient breath operated device rather than the normal hand

-6-

operated device. Such devices are available commercially such as those under the trade mark "Easi-Breathe".

-7-

Claims:

1. A medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.
2. A medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.
3. A formulation as claimed in claim 1 or claim 2, wherein the medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.
4. A formulation as claimed in claim 3, where the medicament is ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropandamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, orciprenaline, salbutamol, salmeterol, sodium cromoglycate, fluticasone, beclomethasone or similar molecule and any physiologically acceptable salt, solvate or ester of such compound.
5. A formulation, as claimed in claims 1-3, where the medicament is a salt of salbutamol.
6. A formulation, as claimed in claims 1-3, where the medicament is a salt of formoterol (sometimes called eformoterol).
7. A formulation according to any of claims 1 to 5, wherein the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.
8. A formulation according to any of claims 1 to 5,

-8-

where the co-solvent level is 10-15%.

9. A formulation according to any of claims 1-5, wherein the polar co-solvent is ethanol.

10. A canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

11. A canister according to claim 9, fitted into an adaptor with an aperture of 100-300 microns.

12. A product according to claims 9 and 10 where the medicament is as per claim 4.

13. A product according to claims 9-11, where the medicament is a salt of salbutamol.

14. A product according to claims 9-11, where the medicament is a salt of formoterol.

15. A canister according to claims 9 and 10, which is actuated by a breath operated device.

16. A product according to claim 15, where the medicament is a salt of salbutamol.

17. A product according to claim 15, where the medicament is a salt of formoterol.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/GB 97/01502

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/12

According to International Patent Classification (IPC) or to both national classification and IPC ⁶

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 93/11 745 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-15. --	1-5, 7-10
A	WO, A, 93/11 743 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-21. --	1-5, 7-10
A	WO, A, 94/03 153 (GLAXO GROUP LIMITED) 17 February 1994 (17.02.94), abstract; claims 1-12. --	1-5, 7-10
A	WO, A, 94/13 262 (JAGER et al.) 23 June 1994 (23.06.94), abstract; claims 1-38,	1-5, 7-9

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search
03 September 1997

Date of mailing of the international search report

26.09.97

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

SCHNASS e.h.

INTERNATIONAL SEARCH REPORT

-2-

International Application No
PCT/GB 97/01502

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>especially claim 4.</p> <p>-----</p>	

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der in obgenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

to the International Search
Report to the International Patent
Application No.

PCT/GB 97/01502 SAE 162218

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

[illegible]

[illegible]